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Hemiparetic Stroke Alters Vastus Lateralis Myosin Heavy Chain Profiles Between the Paretic and Nonparetic Muscles

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Abstract

Skeletal muscle phenotype alterations following hemiparetic stroke contribute to disabilities associated with stroke. The phenotypic response following stroke is undefined. This investigation examined the myosin heavy chain (MHC) composition of the vastus lateralis (VL) of stroke survivors in paretic (P) and nonparetic (NP) muscle. Protein obtained from VL of 10 stroke survivors was isolated and purified, and MHC gel electrophoresis was performed. The MHC bands were quantified, and a paired sample two-tailed *T test with significance set at* $p \leq 0.05$ was performed. MHC I expression was significantly less in P versus NP VL (.93 vs. 1.00 arbitrary units [AU]). Significantly more IIx MHC was found in the P versus NP VL (1.33 vs. 1.0). No significant differences in type IIa MHC (1.07 P vs. 1.00 NP) were found. These changes in MHC composition suggest an alteration in muscle function due to stroke or the altered activity patterns of muscle following stroke.

Keywords

myosin heavy chain; hemiparetic stroke; skeletal muscle fiber type; vastus lateralis

INTRODUCTION

On average, 800,000 Americans will suffer a stroke in a given year. Strokes occur frequently (every 40 seconds in the United States), and it is estimated that stroke-related medical care and disability will cost America over \$65.5 billion in 2008. In fact, stroke is the number three cause of death in the United States behind heart disease and cancer (American Stroke Association 2008). Clearly stroke is a leading cause of disability as evidenced by the fact that over two-thirds of stroke survivors report chronic functional deficits (Gresham, Fitzpatrick, et al. 1975; Gresham, Phillips, et al. 1979; Williams, Jiang, et al. 1999). While upper motor neuron deficits are the primary clinical finding after stroke, it is becoming clear that skeletal muscle is a leading target of secondary injury. Alterations in skeletal muscle likely contribute to a variety of maladies such as insulin resistance, type II diabetes, cardiovascular disease, recurrent stroke, and functional decline (Roth 1993; De Deyne, Hafer-Macko, et al. 2004; Kernan and Inzucchi 2004; Ivey, Ryan, et al. 2006; Vermeer, Sandee, et al. 2006).

There are a number of potential reasons for these muscular adaptations that occur poststroke. After a stroke, survivors lead a more sedentary lifestyle and have altered gait patterns with reduced weight bearing, which can impact skeletal muscle. The stroke also alters neural activation of the hemiparetic side, causing muscle weakness and spasticity. These alterations include muscular atrophy (Ryan, Dobrovolny, et al. 2002), increased intramuscular fat (Ryan, Dobrovolny, et al. 2002), and a shift toward a fast myosin heavy chain (MHC) profile (De Deyne, Hafer-Macko, et al. 2004). Clearly, muscle abnormalities have potential implications for stroke survivors since fast MHC fibers are more fatigable and use primarily anaerobic metabolism as compared with slow MHC. The slow MHC that takes up glucose in response to insulin signaling may be replaced by fast MHC fibers that take up glucose in response to muscle contraction in a leg with reduced weight bearing. This alteration in MHC likely contributes to the high prevalence of insulin resistance/type II diabetes following stroke (Daugaard and Richter 2001).

It previously has been reported that muscle fibers can alter their MHC content in response to environmental stimuli such as disuse, exercise, electrical stimulation, and altered neural innervation patterns (Bottinelli, Canepari, et al. 1994; Baldwin 1996; De Deyne, Hafer-Macko, et al. 2004). We previously identified an increased proportion of fast MHC isoforms in the paretic vastus lateralis (VL) compared to nonparetic (NP) VL of stroke survivors (De Deyne, Hafer-Macko, et al. 2004). Only fast and slow MHC, however, previously were identified. Since there are two major fast phenotypes, the intermediate IIa and the fast IIx, it is unknown whether the loss of type I fibers in paretic muscles was primarily due to the gain of IIa or IIx fibers. This is important since type IIx are the most fatigable fibers (Vescovo, Ambrosio, et al. 2001) due to their metabolic profile, and are the most insulin resistant human MHC fiber type (Daugaard and Richter 2001). Fast fiber types previously have been correlated to type II diabetes (Rabøl, Boushel, et al. 2006). Therefore, the purpose of this investigation was to identify MHC differences in the P and NP VL of stroke survivors. We hypothesize that the paretic leg muscle would have decreased type I and increased IIx MHC composition.

METHODS

Men and women ($N = 12$) aged 50 to 80 years with residual mild–moderate hemiparetic gait from an ischemic hemorrhagic stroke were recruited for this study of skeletal muscle phenotype alterations following stroke. Individuals had gait asymmetry with preserved capacity for ambulation with or without assistive devices, such as ankle foot orthosis and/or a cane or walker. All conventional rehabilitation therapy was completed more than 12 weeks before study entry, and neurological deficits were stable for more than 8 weeks. Chronic stroke (>6 months after stroke onset, latency range 7 to 156 months) was selected to ensure stability of

the residual hemiparetic gait deficits and avoid any potential confounds of early neurological recovery or from intercurrent rehabilitation therapy on skeletal muscle structure and function (Wade and Hewer 1987).

Participants who gave written informed consent for bilateral VL muscle biopsies were randomly selected from our larger chronic stroke population participating in our rehabilitation programs. Exclusion criteria included medical conditions that limit mobility and participation in exercise programs, recent (<3 weeks) infection or inflammation, anti-inflammatory medications, anticoagulation, or known muscle disease. Subjects underwent comprehensive medical history and routine medical and neurological examinations. Cardiovascular fitness levels (peak VO_2 levels) were measured by open circuit spirometry. Functional and mobility testing included the following: a 48-hour recording of home and community ambulatory activity recorded by diary, a computerized step activity monitor (SAM), and the mean of three 10-meter walks indexing self-selected walking speed (SSWS) as an index of gait deficit severity (Macko, DeSouza, et al. 1997). Glucose status data also were collected as subjects were classified as normal glucose tolerant, impaired glucose tolerant, or type II diabetes mellitus. This was done according to medical history and prescribed medications, fasting glucose, and oral glucose tolerance test (in nondiabetic participants) results. Subjects were classified according to the American Diabetes Association standards, where type II diabetes was classified as fasting glucose >126 mg/dl and a 2-hour oral glucose tolerance test glucose level of >200 mg/dl. Impaired glucose tolerance was classified as a fasting glucose between 100–126 mg/dl and a 2-hour oral glucose tolerance test glucose level between 140–200 mg/dl. The University of Maryland Institutional Review Board approved all aspects of this study.

Bilateral VL muscle biopsies were obtained under local anesthesia using a 5 mm Bergström needle (Stille-Werner, St. Paul, MN) using the methods previously described by Hennessey et al. (Hennessey, Chromiak, et al. 1997). Briefly, the skin was cleaned with alcohol and prepared with an iodine solution, then anesthetized locally with 1% lidocaine. Biopsy samples were obtained from the vastus lateralis, approximately 12–13 cm above the patella on the anterolateral aspect of the thigh using a Bergstrom needle (Stille-Werner, Ronkonkoma, NY). All VL samples were immediately freeze clamped in liquid nitrogen and stored in a -80°C freezer until assay.

All samples were homogenized in RIPA Protein Extraction Buffer (Mbiotech, AXXORA, LLC, San Diego, CA; 98% RIPA, 1% Sigma Protease Inhibitor [St. Louis, MO] and 1% Pierce Phosphatase Inhibitor Cocktail [Rockford, IL]) at a ratio of 150 μl of buffer per 10 mg of tissue on ice. Next, samples were homogenized using an IKA S10N-5G blade (Clarkson Labs, Chula Vista, CA) on ice until completely pulverized. All samples then were agitated on ice for 30 minutes. Samples then were centrifuged (Beckman, Microcentrifuge R, Fullerton, CA) at 12,000 g for 10 minutes. The supernatant was collected and put in separate tubes, and a 20 μl aliquot was taken for immediate protein concentration analysis, while the remainder of the sample was stored at -80°C until assay.

Protein concentration was determined using the Pierce BCA Protein Assay Kit (Rockford, IL) per manufacturer's instructions. Each sample was run in triplicate. Next, samples were diluted with deionized distilled water to a concentration of 0.2 $\mu\text{g}/\mu\text{l}$. Samples then were placed in a 95% Laemmli Buffer (Biorad, Hercules, CA) and 5% 2-mercaptoethanol (Bio-Rad, Hercules, CA) to a final concentration of 0.1 $\mu\text{g}/\mu\text{l}$. Finally, all samples were boiled in the buffer for 10 minutes. All samples then were frozen at -80°C until gel electrophoresis.

Myosin heavy chains (MHC) were separated by gel electrophoresis using previously described methods (Talmadge and Roy 1993). MHC was separated in an 8% acrylamide/bisacrylamide gel containing 2.64 ml acrylamide/bis, 30%, 1.33 ml 1.5M tris-HCL, pH 8.8, 4.4 ml 68.16%

glycerol, 1 ml 1M glycine, 200 μ l 20% SDS, 370 μ l dd water, 50 μ l 10% APS, 5 μ l TEMED. The stacking gel was a 4% acrylamide/bisacrylamide gel containing 0.66 ml acrylamide/bis, 30%, 0.70 ml 1.5M tris-HCL, pH 6.8, 2.25 ml 68.16% glycerol, 0.04 ml 0.5M EDTA, 0.1 ml 20% SDS, 1.05 ml deionized distilled water, 100 μ l 10% APS, 5 μ l TEMED. The upper chamber running buffer contained 100 mM TRIS base, 150 mM glycine, and 0.1% SDS. The lower chamber buffer was made by diluting the upper chamber buffer 1:1 in deionized distilled water. For each sample, 10 μ l (at a concentration of 0.1 μ g/ μ l) was loaded onto a gel in triplicate and run for 28 h at 150V in an Invitrogen Surelock Xcell (Carlsbad, CA). The MHC bands were visualized using Bio-Rad's (Hercules, CA) Silver Stain kit per manufacturer's instructions. Gels were photographed using Bio-Rad's Versa Doc Imaging System Quantity One (Hercules, CA), and band intensity was determined using FluorChem (Alpha Innotech Corp., San Leandro, CA).

The data were analyzed for statistical significance by two-tailed Student's *t* test with $p \leq 0.05$ set a priori. Since each sample was run in triplicate, an average optical intensity, controlling for background, was obtained for each MHC sample.

RESULTS

There were no significant clinical (VO₂ peak, activity level) or demographic (age, BMI) differences between the subset of individuals used in the current study compared with our larger cohort of chronic stroke population. Subject descriptive data are presented in Table 1 and illustrate the impact of stroke on activities of daily living and functional performance measures such as walking speed and VO₂ peak. Since MHC phenotype previously has been associated with diabetes (Rabøl, Boushel, et al. 2006), MHC data were correlated with glucose status results. No significant correlations, however, were found between MHC type and glucose status (−.037 for type I MHC and .210 for IIx MHC).

There were no significant differences in the protein concentration (all values are mean $\pm$ SEM) of the paretic VL (4722 $\pm$ 294 mg/g) and the nonparetic VL (4511 $\pm$ 360 mg/g). All values were corrected for both gel background intensity and normalized to the nonparetic leg. Significant differences were noted between the P and NP limbs in proportion of type I MHC (all values are mean $\pm$ SEM, P 0.93 $\pm$ 0.36, NP 1.00 $\pm$ 0.37, $p < 0.04$) and type IIx MHC (P 1.33 $\pm$ 0.40, NP 1.00 $\pm$ 0.37, $p < 0.0004$). Figure 1 contains a representative image of VL MHC composition on a gel from P and NP samples. This data are graphically shown in Figure 2. In the current study across all subjects, the P VL was 39.73% $\pm$ 2.95% type I, 34.00% $\pm$ 3.33% type IIa, and 26.66% $\pm$ 4.63% type IIx, while the NP VL was 47.90% $\pm$ 3.68% type I, 34.45% $\pm$ 2.29% type IIa, and 17.65% $\pm$ 2.97% type IIx. Please see Figure 3 for a graphic representation of MHC fiber isoform by percentage in the paretic and nonparetic VL.

DISCUSSION

The major finding of this study is that there is an apparent shift from the slow oxidative fibers of type I MHC to faster glycolytic fibers of type IIx MHC following stroke. Clearly, this has major clinical implications in regards to the deficits commonly observed in stroke patients, as well as the potential importance of exercise to help these subjects overcome the poststroke modifications. Previously it has been suggested that fiber type transition likely occurs from I to IIa or IIa to IIx (or in reverse due to training). Moreover, it does not appear as though a type I can go directly to IIx or from IIx to type I (Powers, Criswell, et al. 1992).

Stroke subjects offer an interesting perspective to study the biologic changes in the paretic muscle since each subject's nonparetic leg muscle can serve as its own internal control. The use of bilateral muscle samples eliminates individual variation in variables such as diet, activity

level, or genetics, which is a considerable limitation of analysis of human tissues using separate subjects for control and experimental biopsies.

For this study, we define chronic stroke as ≥ 6 months following stroke onset. The 6-month timepoint to define chronic stroke was selected since traditional physical therapy generally is completed and neurological deficits traditionally are stable (Jorgensen, Nakayama, et al. 1995). While stroke-induced muscle changes are not well defined, muscle changes have been well documented following spinal cord injury, another type of upper motor neuron injury. Castro et al. reported changes in vastus lateralis MHC composition over 6 months following spinal cord injury. These changes include significant fiber atrophy (as much as 56%), and decreased force production during electrical stimulation (Castro, Apple, et al. 1999). Burnham et al. also studied skeletal muscle changes after human spinal cord injuries from 2 weeks through 219 months postinjury. They found that MHC composition remained stable for 1 month postinjury, but over 1 to 20 months after spinal cord injury, the proportion of slow MHC decreased and the proportion of fibers coexpressing fast and slow MHC increased. By 70 months postinjury, the MHC composition had stabilized (Burnham, Martin, et al. 1997). Therefore, it is a possible limitation that some of the subjects may not be completely stable in regards to their MHC isoform expression.

The changes in MHC composition of the P limb versus the NP limb are worth noting. The VL normally is considered a mixed muscle, containing equal amounts of fast and slow MHC (De Deyne, Hafer-Macko, et al. 2004). Figure 2 illustrates that the VL of stroke survivors' paretic side is 39% type I MHC and 27% type IIx MHC. This is compared with the nonparetic VL, which was 48% type I MHC and 18% type IIx MHC. Compounding this is the fact that our laboratory has previously reported significant muscle atrophy in the hemiparetic limb (20% lower in P), as well as increased intramuscular fat (Ryan, Dobrovolsky, et al. 2002). Not only have stroke survivors' muscles become more fatigable, but also overall muscle mass is decreased, clearly affecting their activities of daily living. The fact that stroke subjects' paretic side has a greater overall proportion of type IIx MHC, as evidenced by gel electrophoresis, coupled with reduced muscle mass, is quite troubling in terms of both muscle fiber fatigability and glucose tolerance status. In addition, this has potential clinical implications in regards to fatigue and diabetes based on the characteristics of type IIx MHC. While correlational data in the present study did not show any significance between glucose tolerance status and MHC fiber type, this still holds possible clinical relevance. In the current study, 70% of all subjects were either diabetic or had impaired glucose tolerance. With a sample size of only 10 subjects, 3 of which had normal glucose tolerance, statistical differences would be difficult to detect. Therefore, a larger sample size in future studies may reveal statistical differences. The current study revealed 70% of subjects had impaired glucose metabolism, however, compared with ~20% type II diabetes mellitus in a "normal" older (~65 years) adults (Ivey, Ryan, et al. 2006), highlighting the need for future study in this area.

MHC alterations have been reported in a variety of disease states (Andersen 2003; Andersen, Mohr, et al. 1996; Balagopal, Rooyackers, et al. 1997; Baldwin 1996; Castro, Apple, et al. 1999; De Deyne, Hafer-Macko, et al. 2004; Hutchinson, Linderman, et al. 2001; Ryan, Dobrovolsky, et al. 2002); however, the current study found intraindividual differences from the paretic versus the nonparetic leg muscle. Aging appears to be a major stimulus for a fiber type shift, as older individuals tend to lose type I fibers (Andersen 2003). Patients with peripheral arterial disease have an increased proportion of type IIx fibers in the gastrocnemius muscle compared with age and body composition matched controls, but no differences in other muscle fiber types are reported (McGuigan, Bronks, et al. 2001). Additionally, patients with multiple sclerosis have higher percentages of type IIa/IIx fibers than non-neurological disease controls (Kent-Braun, Ng, et al. 1997). These results are consistent with the current study.

The potential impact of this finding on diabetes cannot be ignored. An increased proportion of fast MHC has been linked to diabetes (Bauman and Spungen 2000). It is estimated that as many as 70%–85% of all stroke survivors have either diagnosed diabetes or impaired fasting glucose levels (Ivey, Ryan et al. 2006; Kernan and Inzucchi 2004). While no known direct cause and effect has been found between stroke and diabetes, a strong correlation exists between the two. Whether stroke patients develop diabetes after the stroke, or whether diabetes contributes to the stroke, remains to be elucidated. Additionally, how much of a loss in type I MHC contributes to these factors warrants further investigation.

There is promise that some of the MHC abnormalities can be corrected. Several investigators have found that skeletal muscle with phenotypic abnormalities can adapt to the stimulus presented and revert toward a more normal phenotype with various interventions such as electrical stimulation or exercise (Puhke, Aunola, et al. 2006; Short, Vittone, et al. 2005; Yarasheski 2003). In other words, there tends to be an increase in type I MHC. Our laboratory has shown that treadmill exercise improves both cardiovascular fitness (Macko, Ivey, et al. 2005), strength, and spasticity (Smith, Silver, et al. 1999) in patients. Whether these exercise-mediated improvements are at the level of the skeletal muscle is currently under investigation.

In conclusion, MHC isoform profiles significantly differ between the P and NP leg of stroke survivors. Since type I fibers are the most oxidative, loss of these fibers could explain the fatigue and decrease in $\text{VO}_{2\text{peak}}$ measures seen in stroke patients compared with control patients. Additionally, type I MHC are responsible for insulin-mediated glucose uptake, while the fast MHC are the least insulin sensitive phenotype (Daugaard and Richter 2001). This may in part explain why so many stroke survivors have impaired glucose tolerance and type II diabetes. These results provide a rationale for stroke survivors to be involved in aerobic exercise training. Future studies should focus on the molecular and mechanistic regulation of these MHC transformations in the paretic leg muscle, and possible exercise training interventions may reverse these phenotype alterations. Additionally, future studies examining MHC transformations as they relate to individual subject's glucose uptake and insulin receptor activity should be examined as well to further establish a role for MHC in regards to the potential for diabetes. Finally, the mechanism of these changes in proportion from type I MHC into IIa MHC and type IIa MHC into IIx MHC warrants further investigation as well.

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FIGURE 1.

A representative MHC gel of the vastus lateralis (VL) of a subject's paretic (P) and nonparetic (NP) fiber type composition.

FIGURE 2.

A bar graph representing the mean $\pm$ SEM (expressed as % of NP) for all MHC isoforms (I, IIa, and IIx) across all subjects. Significant difference between the P and NP at $p \leq 0.05$.

FIGURE 3.
A representation of MHC fiber type isoform percentage by subject condition.

TABLE 1**Subject Characteristics**

	Present MHC study	Hemiparetic stroke exercise study
Subjects	12	72
Age (Years)	65.4 ± 1.5	63.6 ± 1.1
Percent Male	50%	46%
Latency (in months)	75.7 ± 28.8	50.8 ± 5.9
Stroke Hemisphere	58% Left	50% Left
Body Mass Index (kg/m ²)	31.0 ± 2.5	28.6 ± 2.7
VO ₂ Peak (ml/kg/min)	12.6 ± 1.0	12.8 ± 0.5
SAM (steps /48 hours)	3956 ± 765	4038 ± 362
SSWS (m/s)	1.0 ± 0.2	1.3 ± 0.1
Impaired Glucose Tolerance or Diabetes	58%	70%

All values are either the percentage of people who express a given trait, or are mean ± SEM. SAM is a 48-hour step activity monitor, and SSWS is self-selected walking speed. The hemiparetic stroke exercise study data are taken from our larger cohort of subjects.